PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
29367		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL2005/000196	16/02/2005	16/02/2004
Applicant		
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL2005/000196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/05 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW pharmaceuticals, THC:CBD." DRUGS IN R&D. 2003, vol. 4, no. 5, 2003, pages 306-309, XP009048624 ISSN: 1174-5886 page 307, 4th full paragraph	1-5
X	WO 99/53917 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SEC) 28 October 1999 (1999-10-28) page 3, line 26-30; page 10, line 31-34; page 11, line 12-27; page 23, line 17-19	1-18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2005	21/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, M

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL2005/000196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/063847 A (GW PHARMA LIMITED; WHITTLE, BRIAN; JAVID, FARIDEH, AFSHIN) 7 August 2003 (2003-08-07) page 1, line 18-25; page 2, line 28 - page 3, line 21	1-5
Y	WEISS LOLA ET AL: "Cytokine production in Linomide-treated nod mice and the potential role of a Th (1)/Th(2) shift on autoimmune and anti-inflammatory processes." CYTOKINE. 21 JUL 2002, vol. 19, no. 2, 21 July 2002 (2002-07-21), pages 85-93, XP002330933 ISSN: 1043-4666 figure 1; figure 4; page 87-91, paragraph entitled "Discussion"	1-23
Y	SRIVASTAVA M D ET AL: "DELTA 9 TETRAHYDROCANNABINOL AND CANNABIDIOL ALTER CYTOKINE PRODUCTION BY HUMAN IMMUNE CELLS" IMMUNOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, vol. 40, no. 3, October 1998 (1998-10), pages 179-185, XP000957596 ISSN: 0162-3109 page 183-184, paragraph entitled "Discussion"	1-23

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL2005/000196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9953917 A	28-10-1999	AU 766988 B2	30-10-2003
		AU 3864699 A	08-11-1999
		CA 2329626 A1	28-10-1999
		EP 1071419 A1	31-01-2001
		JP 2002512188 T	23-04-2002
		WO 9953917 A1	28-10-1999
		US 6630507 B1	07-10-2003
WO 03063847 A	07-08-2003	EP 1482917 A1	08-12-2004
		GB 2384707 A	06-08-2003
		WO 03063847 A1	07-08-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	21 June 2005 (1)
see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/IL2005/000196	International filing date *(day/month/year)* 16.02.2005
Priority date *(day/month/year)* 16.02.2004	
International Patent Classification (IPC) or both national classification and IPC A61K31/05, A61P3/10	
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE...	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Borst, M

Telephone No. +49 89 2399-8648

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000196

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,11,19 (examination and search of said claims only for the part relating to compounds according to formula (I))

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,11,19 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,11,19

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-23
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Clarity (Article 6 PCT)

Present independent claims 1, 11, 19 are not clear, because the term "cannabidiol compound" has not a clearly defined meaning generally accepted in the art.
Therefore, the search and substantive examination will be performed on the basis of the compounds according to formula (I).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Documents (D) considered to be relevant to novelty and inventive step

D1: "Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW pharmaceuticals, THC:CBD." DRUGS IN R&D. 2003, vol. 4, no. 5, 2003, pages 306-309, XP009048624 ISSN: 1174-5886

D2: WO 99/53917 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SEC) 28 October 1999 (1999-10-28)

D3: WO 03/063847 A (GW PHARMA LIMITED; WHITTLE, BRIAN; JAVID, FARIDEH, AFSHIN) 7 August 2003 (2003-08-07)

D4: WEISS LOLA ET AL: "Cytokine production in Linomide-treated nod mice and the potential role of a Th (1)/Th(2) shift on autoimmune and anti-inflammatory processes." CYTOKINE. 21 JUL 2002, vol. 19, no. 2, 21 July 2002 (2002-07-21), pages 85-93, XP002330933 ISSN: 1043-4666

D5: SRIVASTAVA M D ET AL: "DELTA 9 TETRAHYDROCANNABINOL AND CANNABIDIOL ALTER CYTOKINE PRODUCTION BY HUMAN IMMUNE CELLS" IMMUNOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, vol. 40, no. 3, October 1998 (1998-10), pages 179-185, XP000957596 ISSN: 0162-3109

The numbering will be adhered to in the rest of the procedure.

1. Novelty (Article 33(2) PCT)

1.1. The subject-matter of present claims 1-5 is not new in the light of D1.
D1 (page 307, 4th full paragraph) discloses the use of a combined preparation of

CBD and THC for the treatment of patients with peripheral neuropathy secondary to diabetes mellitus.

The wording of the claims does not exclude the co-administration of further drugs apart from CBD. Moreover, the therapeutic administration to (i) patients with peripheral neuropathy secondary to diabetes mellitus cannot be distinguished from a therapeutic administration to (ii) patients with diabetes, since patient group (i) falls within patient group (ii).

1.2. The subject-matter of present claims 1-18 is not new in the light of D2.
D2 (page 3, line 26-30; page 10, line 31-34; page 11, line 12-27; page 23, line 17-19) discloses the use of CBD for its antioxidant property for the treatment of oxidative associated diseases including autoimmune diseases, such as diabetes. Autoimmune diabetes is type 1 diabetes and includes insulitis.

1.3. The subject-matter of present claims 1-5 is not new in the light of D3.
D3 (page 1, line 18-25; page 2, line 28 - page 3, line 21) discloses the use of a cannabis extract rich in CBD for the treatment of nausea occurring in diabetes. Therapeutic use in (i) patients with nausea occurring in diabetes mellitus cannot be distinguished from a therapeutic use in (ii) patients with diabetes, since patient group (i) falls within patient group (ii).

2. Inventive step (Article 33(3) PCT)

2.1. The subject-matter of present claims 1-5, 7-10 does not involve an inventive step, because the problem of providing an effective treatment is not solved for the whole scope of the claims.
The invention on file is based on the finding that CBD has positive effects in NOD mice. As stated in the application itself (cf. page 17, line 31 - page 18, line 2) NOD mice develop spontaneous autoimmune diabetes and, therefore, represent an experimental model for insulin-dependent diabetes mellitus. Thus, the experimental evidence provided is clearly limited to type 1 diabetes and there are no facts provided supporting an extrapolation to type 2 diabetes. Thus, any subject-matter directed to or including the treatment of type 2 diabetes canot be considered as being solved and, hence, as involving an inventive step.

2.2. The subject-matter of claims 1-23 does not involve an inventive step in the light of D4 and D5.
Like the application on file D4 deals with the treatment of autoimmune diabetes and

insulitis in NOD mice. According to D4 (figure 1; figure 4; page 87-91, paragraph entitled "Discussion") linomide reduced inter alia levels of TNF alpha and IFN gamma and prevents autoimmune insulitis and diabetes mellitus in NOD mice. D4 concludes that "Linomide and/or non-immunosuppressive agents with a similar mode of action may prove to be promising tools for the treatment of type I diabetes mellitus". D4 does not disclose a CBD compound.

The objective technical problem to be solved in the light of D4 was to provide further agents with a mode of action similar to linomide and effective in the treatment of type I diabetes mellitus.

D5 (page 183-184, paragraph entitled "Discussion") discloses a mechanism of action similar to that of linomide for CBD in autoimmune/inflammatory diseases by inhibitiion of TNF alpha and IFN gamma and, there with, directly points to the use of CBD for the treatment of type 1 diabes, insulitis and the protection of transplanted pancreatic cells.

Conclusion

In view of the far-reaching anticipation by the prior art cited it is at present apparent which part of the application could serve as a basis for a new, allowable claim. In any case limitation to type 1 diabetes appears to be inevitable.